TITLE: EPA's Children's Environmental Health Roadmap: applying the 21st century vision to prenatal development

AUTHORS: Sipes, Nisha S.[1]; Knudsen, Thomas B.[1]; Firestone, Michael P.[2]; Cohen-Hubal, Elaine[3]
INSTITUTIONS: 1. National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC, United States. 2. Office of Children's Health Protection, U.S. Environmental Protection Agency, Washington D.C., United States. 3. Chemical Safety for Sustainability Research Program, U.S. Environmental Protection Agency, Research Triangle Park, NC, United States.

ABSTRACT

Understanding the complex relationships between environmental exposures and early life susceptibility in assessing the risk for adverse pregnancy outcomes requires advanced knowledge of biological systems. This broad research is a driver for the Children's Environmental Health roadmap which outlines research objectives using a systems approach to generate predictive models that will inform risk assessment of childhood and adult diseases and adverse outcomes of developmental origins. The Roadmap research will integrate biomonitoring data for child exposure to environmental contaminants, epidemiological studies associating exposures with adverse outcomes, and biological models and empirical studies investigating the plausible mechanisms of developmental toxicity. This 21st century vision for children's health aims to apply systems biology approaches to integrate and utilize information in an Adverse Outcome Pathway (AOP) framework for developmental toxicity. This includes biological information measured in high-throughput and high-content datasets that provide a foundation for in vitro profiling (e.g., ToxCast) and in vivo correlation (e.g., ToxRefDB). Specific chemical-endpoint correlations mined from these complex datasets can often be deconvoluted by existing knowledge from the open literature (e.g., e-libraries and semi-automated text-mining) and biological databases (e.g., www.informatics.jax.org) to build predictive signatures. Modeling the molecular interactions and downstream biological effects as key events in an AOP provides the framework for establishing causality, which can be subjected to simulation models that translate effects across scales of biological organization and function. Parameterizing these models with various forms of data help define critical windows of susceptibility for different exposure scenarios and dosimetry models. Systems-level manipulations coupled with functional studies would then be used to evaluate the validity of the in silico system-level behaviors and evaluate model performance. We have successfully applied this approach for various developmental outcomes (angodysplasias, cleft palate, hypospadias, limb abnormalities). These predictive models demonstrate the utility of the systems biology approach to gain a better understanding of mechanisms behind environmental exposure and adverse developmental outcomes that would not have been fully realized through traditional studies alone. *This abstract does not necessarily reflect US EPA policy.*